REMARKS

Claims 90-177 were pending. Claim 91 has been amended to correct an editorial error, to make its language consistent with that of claim 90. New claim 178, directed to a specific embodiment of the invention, has been added. Support for the new claim can be found, *inter alia*, at paragraphs [0100] and [0102] of the specification. No new matter is added by the amendments made herein.

Following entry of the amendments made herein, claims 90-178 will be pending in the instant application.

INTERVIEW SUMMARY RECORD

Applicant and Applicant's representatives thank Supervisory Patent Examiner Gary Benzion and Examiner Suryaprabha Chunduru for the courtesy of the recent interview in connection with the above-identified application. Pursuant to 37 C.F.R. § 1.133 and M.P.E.P. 713.04, Applicant presents this interview Summary Record of the interview of March 30, 2006 ("the Interview") between Supervisory Patent Examiner Gary Benzion and Examiner Suryaprabha Chunduru, and Applicant's representatives Drs. H. Perry Fell, Adriane M. Antler, Muna Abu-Shaar and David Gay (via telephone), in connection with the above-referenced application. During the Interview, the Office Action dated January 10, 2006 ("Office Action") was discussed.

At the outset, Applicant's representative Dr. Adriane Antler sought clarification regarding whether the rejection over U.S. Patent No. 6,361,944 B1 to Mirkin et al. ("Mirkin") was made under 35 U.S.C. § 103 or 35 U.S.C. § 102(e). Supervisory Patent Examiner Gary Benzion and Examiner Suryaprabha Chunduru clarified that the rejection was an obviousness rejection under 35 U.S.C. § 103.

With respect to the substance of the rejection, Dr. Antler explained the features common to all the independent claims directed to populations of thirty or more unique labels. Dr. Antler also explained why prior art relied upon by the Examiner in the instant Office Action, Mirkin mentioned above and WO 99/52708 by Chandler ("Chandler"), alone or in combination, did not teach or suggest the subject matter of the instant claims. Supervisory Patent Examiner Gary Benzion agreed, subject to a further review of the cited references and

a discussion with Primary Examiner Jeffrey Fredman, that the claims were not made obvious by the prior art cited in the Office Action.

Details of the arguments presented in support of patentability are found hereinbelow.

THE REJECTION UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

The Present Claims

Pending claims 90-156 and new claim 178 are directed to diverse populations of labels. The diverse populations of the invention have several "basic" features in common:

(1) the *populations comprise at least 30* (or, in claim 152, at least 100) *unique labels*, which as defined in the specification (see ¶ [0021] of US20030013091 A1) means that each unique label "has a detectable signal that distinguishes it from other labels in the same mixture." Thus, there are 30 or more labels in the population, each of the 30 or more labels giving rise to a signal that is distinguishable from the other 29 or more labels.

(2) wherein each of said *unique labels comprises a molecule, said molecule comprising a plurality of genedigits* (defined as "region of pre-determined nucleotide or amino acid sequence that serves as an attachment point for a label," see ¶ [0017] of US20030013091 A1), each genedigit being of predetermined sequence. It should be noted that the claims require that the at least two genedigits are in a single molecule.

(3) wherein *at least two* (or, in claim 152, at least 4) of said *genedigits are each attached to a respective anti-genedigit* (defined as "a nucleotide or amino acid sequence or structure that binds specifically to the gene digit," see ¶ [0017] of US20030013091 A1), each said anti-genedigit being *attached to at least one label monomer*.

Thus, pending claims 90-156 and new claim 178 provide for diverse populations of (*e.g.*, 30 or more) labels distinguishable by virtue of the attachment of label monomers to genedigits via the specific binding of anti-genedigits to which the label monomers are attached. The modular permutations of genedigit/anti-genedigit combinations gives rise to diverse populations of unique, *i.e.*, distinguishable, labels, starting even from a small number

of label monomers. The diverse populations of labels can be attached to target-specific sequences to detect analytes of interest. See, *e.g.*, US20030013091 A1 at ¶¶ [0028], [0029] and [0079] and Figure 1. Accordingly, each of the *30 or more* labels in the population are *distinguishable in signal* from the other 29 or more, each label has at least 2 genedigits that are in a *single molecule*, each of the at least 2 genedigits being attached to a label monomer via the anti-genedigits (which are attached to the label monomer).

Pending claims 157-177 are directed to labeling kits useful for generating the diverse populations of the invention.

The Present Rejection

Claims 90-177 are rejected under 35 U.S.C. § 103 as obvious over U.S. Patent No. 6,361,944 B1 to Mirkin et al. ("Mirkin") in view of WO 99/52708 by Chandler ("Chandler").

According to the Examiner, Mirkin teaches:

> ...a diverse population of nanoparticles comprising aggregate probe molecule comprising plurality of genedigits, each genedigit being a predetermined sequence (oligonucleotides) wherein gene digit is attached to an anti-gene digit (complementary sequences or oligonucleotide probe sequences) (see col. 26, line 56-67, vol. 27, line 1-21, col. 18, line 6-17, indicates one type of nanoparticles having oligonucleotide portions (genedigit) complementary to another type of nonoparticles (*sic*) having oligonucleotide sequences (anti-genedigit)).

Office Action at 3. The Examiner has also indicated that Mirkin teaches other aspects of the invention (Office Action at 3-4), but does not teach a diverse population of thirty or more labels. The Examiner then goes on to say that in view of Chandler, which teaches microparticles with multiple fluorescent signals, one of skill in the art would have been motivated

> "to combine the diverse population of molecules comprising genedigits and anti genedigits as taught by Mirkin et al. with an inclusion of unique labels as taught by Chandler et al. to develop a sensitive and improved population of molecules with distinct labels. An ordinary artisan would have had a reasonable expectation of success that such modification of the method taught by Mirkin et al. in a manner as taught by Chandler et al. because Chandler et al. explicitly taught that unique labels or dyes comprise unique emission spectra (see page 6, lines 2-4) which is unique to the specific set or population (see page 23, lines 17-25); unique labels comprise mixture of two or more (64-40,960) different or distinctly labeled particles created through variation of the amount of or type of dye (see page

> 17, lines 28-37, page 18, lines 1-15, page 6, lines 23-33) and such modification of the method is considered obvious over the cited prior art in the absence of secondary considerations."

Office Action at 5.

The Examiner contends that the present claims are obvious over Mirkin in view of Chandler. Applicant submits that the Examiner's assessment of Mirkin and Chandler is in error, and the pending claims are not obvious over the references, as discussed below.

The Law Of Obviousness

To establish a *prima facie* case of obviousness, the teachings of the prior art must provide one of ordinary skill in the art with some suggestion or motivation to make the claimed composition. *In re Rijckaert*, 28 U.S.P.Q.2d 1955, 1956 (Fed. Cir. 1993). For a claimed invention to be deemed obvious in view of a prior art disclosure, the prior art disclosure must, firstly, give rise to a *suggestion of or motivation for* the claimed subject matter. Assuming such a suggestion or motivation is found, and the invention is thus arguably "obvious to try" to achieve, only then does one reach the question of whether one of ordinary skill in the art would have had a reasonable expectation of success in achieving it. *See e.g.*, *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). Both the suggestion of the claimed invention and the expectation of success must be in the prior art, not in the disclosure of the claimed invention. *In re Dow Chemical Co.*, 837 F.2d 469 (Fed. Cir 1988).

"Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field." *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999), abrogated on other grounds, citing to *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983). In particular, the Examiner cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988). Care must be taken to avoid hindsight reconstruction by using Applicant's disclosure "as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result" of the claims in question. *Grain Processing Corporation v. American Maize-Products*

Company, 840 F.2d 902, 907 (Fed.Cir.1988), citing *Orthopedic Equip. Co. v. United States*, 702 F.2d 1005, 1012 (Fed.Cir.1983).

Applicant submits that the Examiner, in raising the obviousness rejections, is employing a hindsight reconstruction without casting her mind to the state of the art at the time of filing the present application. As stated above, such hindsight reconstruction cannot be used for determining obviousness. Neither of the references cited by the Examiner, alone or in combination, suggests or provides motivation for the presently claimed invention, let alone with a reasonable expectation of success. In particular, Mirkin does not suggest more than one unique label containing the basic features described above, *i.e.*, distinguishable in signal from other labels in the population and containing at least two genedigits that are part of the same molecule, each attached to an anti-genedigit to which is attached a label monomer, and Chandler does not suggest *any* such unique label. Each of these references is discussed in turn below to demonstrate that, whether alone or in combination, these references do not provide any suggestion of, or motivation for, the claimed invention.

Mirkin and Chandler Do Not Suggest or Provide Motivation for the Present Invention

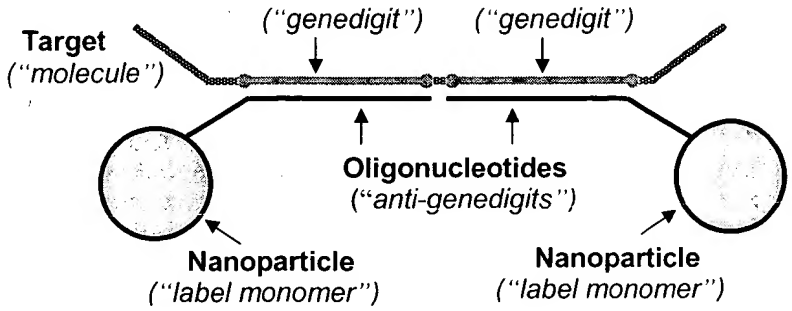
Mirkin

Mirkin generally relates to detection of target nucleic acids using nanoparticle-bound oligonucleotides. According to the teachings of Mirkin, target nucleic acids are detected by an observable change that is a color change, aggregation or precipitation, due to binding of the nanoparticles to the target molecule (see column 20, lines 7-19).

In its simplest embodiment, Mirkin teaches a system for detecting a nucleic acid target using two nanoparticle-bound oligonucleotides, which upon hybridization to the target produce a detectable color change (column 2, lines 5-18; column 20, lines 59-63). For example, hybridization of gold nanoparticle-bound oligonucleotides to a target molecule produces a red-to-purple color change. *See, e.g.*, Mirkin at Figure 6 and legend thereto at column 13, lines 49-62 describing the red-to-purple color change. This basic embodiment of Mirkin is illustrated in Figure 2.

A schematic representation of Figure 2 of Mirkin is presented below. The discussion below shows that, even when analogizing the components of Mirkin's hybridization complex in an attempt to "best fit" it to elements of the present claims, the nanoparticle probe-

hybridization complex of Mirkin is *no more than a single unique label* (as that term is construed in the present claims):



Attempted "Best Fit" of Figure 2 of Mirkin to core features of claims

This complex of Figure 2 produces a single detectable signal, which is generated when the two nanoparticle-bound oligonucleotides bind to the target molecule. See, *e.g.*, column 2 at lines 59-62, which states that an "important aspect of the detection system illustrated in FIG. 2 is that obtaining a detectable change depends on cooperative hybridization of two different oligonucleotides to a given target sequence in the nucleic acid."

When considering the teachings of Mirkin, it is important to note Mirkin's particular definitions of a "type of nanoparticle" and a "type of oligonucleotide." As Mirkin states:

> A "type of" nanoparticles, particles, latex microspheres, etc. having oligonucleotides attached thereto refers to a plurality of nanoparticles having the same type(s) of oligonucleotides attached to them.

Mirkin at column 12, lines 59-62.

> As used herein, a "type of oligonucleotides" refers to a plurality of oligonucleotides having the same sequence.

Mirkin at column 12, lines 57-59.

Accordingly, a "different type of nanoparticle" as used by Mirkin is a particle with an oligonucleotide of a different sequence, not a different label monomer; *i.e.*, "different types" of nanoparticles are *not*, *e.g.*, gold vs. silver vs. copper. Keeping the above definition in mind is necessary to a proper understanding of Mirkin's teachings.

Applicant points out that in contrast to the diversity of labels produced by the present invention, Mirkin does *not* teach making more than one unique probe-target molecule complex that has contains the basic elements of a label of the invention and has a signal distinguishable from any other labels in the population. Indeed, Mirkin teaches many alternatives to the simple 2-oligonucleotide probe system depicted in Figure 2. However, the various embodiments taught by Mirkin relate to *amplification* of the signal resulting from hybridization of nanoparticle-bound oligonucleotides to a single target nucleic acid *in order to increase assay sensitivity*, and not to the creation of multiple distinguishable signals. Thus, Mirkin teaches ways of aggregating and layering "different types of nanoparticles" (as that term is defined above by Mirkin) by additional hybridizations on the type of construct in Figure 2 in order to increase signal intensity to increase assay sensitivity, not to obtain different unique labels (*i.e.*, labels with distinguishable signals). For example, Figure 5 of Mirkin schematizes oligomerization and linking of two "types" of gold nanoparticles, "A" and "B", that differ only in that they are bound to different oligonucleotides, in order to achieve nanoparticle aggregation and amplification of a single signal (see Figure 5 and legend thereto at column 13, lines 44-48).

Mirkin's goal of increasing signal intensity and assay sensitivity is clearly apparent throughout Mirkin. For example, at column 19, lines 39-41, Mirkin teaches that "[t]argeting several portions of a nucleic acid increases the magnitude of the detectable change." Mirkin further states that multiple types of nanoparticle-oligonucleotide conjugates can be produced such that:

> If desired, additional layers of nanoparticles can be built up by successive additions of the first and second types of nanoparticle-oligonucleotide conjugates. In this way, *the number of nanoparticles immobilized per molecule of target nucleic acid can be further increased* with a corresponding increase in intensity of the signal.

Mirkin at column 22, lines 40-45 (emphasis added). *See also* Mirkin at column 24, lines 31-36; column 27, lines 21-27; and column 28, lines 50-55. As made clear by these numerous quoted sections, the purpose of these additional embodiments is to amplify one composite signal from a single target molecule (the signal arising from the binding of numerous nanoparticles), rather than to generate a diversity of distinguishable signals for a diversity of target molecules. Thus, the signal generated and used in Mirkin's assay satisfies a yes or no criterion: is the color change present or not?

With respect to the types of "label monomers" to which the various probe embodiments can be attached, Mirkin teaches at column 16, lines 29-36 a variety of different nanoparticles (*e.g.*, gold, silver, copper) that can be used.[1] While 24 different nanoparticles are listed, importantly, there is no suggestion to create a population of different distinguishable signals from the different nanoparticles. Rather, with two exceptions described below, Mirkin teaches to select and use in any assay mixture only one nanoparticle label monomer at a time, such as gold, which is preferred (column 16, lines 64-65), and teaches how to amplify the signal from that particular nanoparticle. As mentioned above, there are only two exceptions in Mirkin to the foregoing, both of which are discussed immediately below.

The first exception is an embodiment in Mirkin that utilizes two types of label monomers, quantum dots and gold (see section under the heading "Preparation of QD/Gold Assemblies" at column 64 and Figures 27C-D). However, the quantum dot and gold are assembled so as to produce only a single unique label as that term is used in the instant claims, since the signal(s) arising from the gold and quantum dot particles when used as taught by Mirkin are not distinguishable from any other signal arising from something in the assay mixture having the "basic" structural features of a label as claimed (*i.e.*, a single molecule with at least two genedigits attached to respective anti-genedigits attached to label monomers). That is, all complexes having the structural features of a label as claimed have signals arising from both the gold and quantum dot particles and thus are all the same signals and are indistinguishable from each other. Moreover, Mirkin indicates that the "intensity of the plasmon band obscures the UV/Vis signal from the QDs." Mirkin at column 65, lines 5-6.

The second exception to the use in Mirkin of only one label monomer in a particular assay is in the context of the use of fluors, where different types of fluors (or a combination of a metal nanoparticle and a fluor, such as the gold nanoparticle and fluor in Figure 21) are used to achieve one particular color change as the assay indicator. In such embodiments, Mirkin uses fluors bound to oligonucleotides or fluors bound to particles (such as latex beads) in a donor-quenching assay (see, *e.g.*, column 29, lines 3-20; column 30, line 28 through column 32, line 44; Figures 20A and 21) or in a fluorescence resonance energy transfer

[1] Note that these are *not* "different types of nanoparticles" as that phrase is defined in Mirkin, as discussed above.

("FRET") donor-acceptor assay (see column 29, lines 35-37, column 29 line 56 to column 30 line 7 and Figure 20B). In the donor quenching assay , a decrease or increase in signal from the donor fluor (*e.g.*, a respective loss or increase of red) occurs upon hybridization due to the resulting increase or decrease, respectively, in the distance separating the quencher (*e.g.*, the gold nanoparticle) and the fluor; thus, decrease or increase of the donor fluor signal is the assay indicator. In the FRET assay, the appearance of signal from the acceptor fluor (*e.g.*, appearance of red) occurs upon hybridization due to the proximity of the donor fluor to the acceptor fluor; this appearance of the acceptor fluor signal is the assay indicator.

In all these assays involving fluorescent label monomers, no more than a single "unique label" (as that term is construed in the claims) is formed upon hybridization to the target molecule. This is because the hybridization event yields multiple identical structures, and all the identical structures produces an identical signal (a color change). Thus, the structures present in a hybridization assay cannot be distinguished from one another by signal.

Moreover, in the case of the donor quenching assay schematized in Figure 20A, not even a single "label" is formed, as the hybridization results in a double stranded fluorescently-labeled probe-target complex that lacks the plurality of genedigits and anti-genedigits in a single molecule that is mandated by the claims.

Except for the foregoing exceptions, Mirkin teaches to use only one label monomer, *e.g.*, a gold nanoparticle, in any single assay, consistent with its emphasis on amplification of a single signal.

For example, in Figure 13B of Mirkin, immobilized oligonucleotide-bound nanoparticles are hybridized to the target molecule, and additional nanoparticles are layered on the complex through a "nanoparticle linker strand" to generate a nanoparticle-target aggregate (see Mirkin at column 24, lines 37-45). However, all "types" of nanoparticles that are layered and aggregated in Figure 13B are the same label monomer, so none of the hybridization entities in the layering process have distinguishable signals. Accordingly, the assay format of Figure 13B does not generate a plurality of unique labels, each having the basic structural elements of the claims and a distinguishable signal, as required by the claims.

Figure 17 of Mirkin illustrates the hybridization of different "types" of nanoparticles (*i.e.*, of the same label monomer but having oligonucleotides of different sequences attached)

onto a single target molecule (see column 19, lines 37-39; column 21, line 67 to column 22, line 6; and column 39, lines 10-15). The hybridization complexes of Figures 17A and 17B each represent, in the language of the current claims, a single target molecule with two genedigits, each genedigit hybridized to an anti-genedigit bound to a label monomer. The two label monomers bound to the target molecule are the same (*e.g.*, gold), and generate one particular signal. Thus, the complexes of Figures 17A and 17B each yield a single unique label according to the claims. In the hybridization complex of Figure 17C, seven different "types" of nanoparticles are hybridized to the target molecule, each via a different sequence-specific oligonucleotide; however, all the label monomers are the same (*e.g.*, gold), and the entire hybridization complex produces one distinguishable signal, the seven different "types" of nanoparticles functioning only to increase signal intensity of that one signal. Figure 17D and Figure 17E demonstrate the use of connector oligonucleotides, which are used to attach the nanoparticles to the target molecule; however, hybridization of the connector to the target molecule (not depicted in the Figures) still yields no more than one distinguishable signal and therefore, at best, one unique label according to the present claims.

In other permutations, as outlined in Figure 28A, oligonucleotide-bound nanoparticles are aggregrated onto a core in a variety of different ways and used in different assay formats. In particular, a "type" of nanoparticle (attached to oligonucleotide "a" in Figure 28A) is bound to a second "type" of nanoparticle (attached to oligonucleotide "a^1" in Figure 28A) by hybridization of their attached oligonucleotides, forming "core particles," and these core particles in turn are hybridized to yet a third "type" of nanoparticle, whose attached oligonucleotides contain an additional set of target-specific oligonucleotides ("b" in Figure 28A), to form an "aggregate" target-specific probe. In Figure 28B, different "types" of nanoparticles are hybridized to form an aggregate. However, neither the cores, the aggregates nor hybridization complexes containing the cores and aggregates represent more than one unique label of the claims, because *inter alia* they produce only one distinguishable signal. For example, the assay format of Figure 28D generates a hybridization complex comprising one target molecule (containing regions c′ and b′) that is hybridized to one aggregate nanoparticle (through oligonucleotide "b") and one single nanoparticle (through oligonucleotide "c") that is the same label monomer as in the aggregate (see column 27 at lines 48-57). Thus, this complex represents at best one label according to the claims, comprising a single target molecule with two genedigits hybridized to respective anti-

genedigits that are in turn bound to two label monomers, the complex producing one distinguishable signal.

In fact, certain assays disclosed in Mirkin do not result in *any* unique label according to the instant claims, *i.e.*, a label that has a distinguishable signal *and* the structural basic features of the present claims. For example, in Figure 13A, a substrate-bound oligonucleotide is hybridized to target DNA to generate overhang B′. B′ is hybridized to nanoparticles bound to complementary oligonucleotide B. Additional nanoparticles bound to oligonucleotide B′ are further layered on the complexes containing the target molecule. However, in no instance is a "label" according to the claim created, because there is no single molecule at any stage of the layering process that has at least two label monomers, each of which is attached to the single molecule via a genedigit/anti-genedigit interaction.

Similarly, the assay format of Figure 28C does not result in *any* unique label as claimed herein. A substrate-bound oligonucleotide (c) is hybridized to target DNA (containing regions b^1 and c^1) to generate overhang b^1. b^1 is hybridized to an aggregate probe, but no "label" according to the claim is created, because there is no single molecule in the hybridization complex that has at least two label monomers, each of which is attached to the single molecule via a genedigit/anti-genedigit interaction.

The assay format of Figure 28E also does not generate a single unique label according to the claims. In this format, a substrate-bound oligonucleotide (b) is hybridized to target DNA (b′ and c′) to generate overhang c′. c′ is hybridized to a nanoparticle bound to both complementary oligonucleotide c and oligonucleotide a; the signal of this nanoparticle is amplified by binding to a core through oligonucleotide a′. Again, a "label" according to the claim is never created, because there is no single molecule that has at least two label monomers, each of which is attached to the single molecule via a genedigit/anti-genedigit interaction.

Thus, at best, the various embodiments taught by Mirkin result in the formation of at most *one* probe-target hybridization complex having the structural basic characteristics of a label of the invention that produces a distinguishable signal. As set forth by Dr. Antler during the Interview, the same result is reached with *all* of Mirkin's embodiments. Thus, *at best*, Mirkin discloses a single unique label of the invention, and does not teach or suggest creating a population of more than one such "unique label."

Nowhere in the disclosure of Mirkin is there a teaching or suggestion of the idea of generating a diversity of labels in the same population with both the distinguishable signals *and* basic structural features specified in the claims. Mirkin does not teach or suggest creating distinguishable signals generated by a defined structure to detect different target molecules. The purpose of amplification of the signals of Mirkin's "labels" is ease of detection by, *e.g.*, the naked eye. See, for example Mirkin at column 17, lines 4-7 ("For instance, hybridization of oligonucleotides attached to gold nanoparticles with oligonucleotides and nucleic acids results in an immediate color change visible to the naked eye.") and at column 18, lines 41-45 ("The methods of detecting nucleic acids based on observing a color change with the naked eye are cheap, fast, simple, robust (the reagents are stable), do not require specialized or expensive equipment, and little or no instrumentation is required.") Thus, Mirkin's approach asks the question, "do I observe a color change that is indicative of the presence of a target molecule?" Accordingly, Mirkin does not provide any motivation for producing a population comprising a plurality of distinguishable labels as claimed herein. If anything, Mirkin indicates at column 65, lines 5-6 that signals from multiple label monomers cause interference with one another.

Therefore, there is no teaching or suggestion in Mirkin of a population of thirty or more (as claimed in claims 90-94 and 151) or one hundred or more (as claimed in claim 152) unique labels, each comprising a molecule with a plurality of genedigits, in which at least two genedigits (or, in the case of claim 152, at least four genedigits) are each attached to a respective anti-genedigit, each anti-genedigit being attached to at least one label monomer, as required by the claims. Nor does Mirkin even suggest how such a diverse populations of 30 or more unique labels, *i.e.*, each distinguishable from the other 29 or more, can be achieved.

Thus, Mirkin does not teach or suggest the subject matter of any of independent claims 90-94, 151 and 152.

With respect to claim 157, Mirkin does not teach or suggest a labeling kit comprising in one container thirty or more unique molecules with a plurality of genedigits of predetermined sequence and in one or more other containers a plurality of respective anti-genedigits, each attached to at least one label monomer, for the same reasons as discussed above. Thus, Mirkin also does not teach or suggest the subject matter of independent claim 157.

For the foregoing reasons, the dependent claims are also nonobvious over Mirkin.

Chandler

Chandler does not remedy the deficiencies of Mirkin. Chandler discloses a multiplicity of labels, but these are not the unique labels defined by the claims, as discussed below.

Chandler discloses dye-labeled nanoparticles attached to microparticles or dye-labeled microparticles. Chandler is able to generate a large number of distinguishably labeled microparticles by using combinations of different discriminators, such as "particle physical property, particle concentration, spectral property, dye type, dye concentration, label type, and combinations thereof." See Chandler at Abstract.

Chandler teaches the use of its microparticles to label fluids, solids and gasses, focusing on liquids, for example to track their flow (Chandler at page 22, lines 10-16) or to identify patient samples (Chandler at page 20, lines 28-30). Chandler labels the desired substances by simply adding the desired particles to the substance (Chandler at page 23, lines 35-36) where they remain inert (see, *e.g.*, Chandler at page 24, line 3). The labeled microparticles thus simply float around, *e.g.*, in the liquid. Chandler decodes the different distinguishable labels, for example, by then separating the particles from the liquid (see Chandler at page 25, lines 23-25). There is no specific attachment of the microparticles or nanoparticles of Chandler to the substance being identified, for example through a genedigit/anti-genedigit system.

Chandler does not disclose attaching label monomers to a single molecule through at least two sites of predetermined sequence (such as a genedigit). In Chandler, the label monomers are non-specifically and randomly attached to the nanoparticles or microparticles. For example, Chandler advocates that his method "allows for a highly reproducible process in which two or more dyes of independent concentration are *absorbed* [*i.e.*, non-specifically bound] into or onto each particle, resulting in multiple spectrally distinct fluorescent signals corresponding to the number of different dyes present in or on the particle" (Chandler at page 13, lines 16-19). Other embodiments for attachment of label monomer to nanoparticles and microparticles, such as cross-linking, are disclosed at page 8, line 31 through page 9, line 18 of Chandler. Nowhere in Chandler is there is description or a suggestion of a modular, sequence-specific genedigit/anti-genedigit attachment of a label monomer to a nanoparticle or

microparticle. Thus, Chandler does not even teach or suggest a single label of the present claims, and thus does not remedy the deficiencies of Mirkin.

Additionally, Mirkin's hybridization complexes are formed by binding of nanoparticle-bound oligonucleotides to a target molecule to generate a binary (on/off color change) signal, whereas Chandler's labeled nanoparticle and microparticles, as discussed above, are used as inert labels that are added to the substance being labeled, generally a fluid. Therefore, the motivation to combine the teachings of Mirkin and Chandler is lacking. Also, because Chandler does not teach binding his distinguishable labels to a substance, it is unclear how or if Chandler's labeled microparticles can be used in conjunction with Mirkin's hybridization-created complexes to achieve more than one label having both the distinguishable signal and structural features of Applicant's claims.

There is also no motivation to combine the teachings of Mirkin with Chandler, because if Chandler's different labels were used in Mirkin's assays, it would be counter to the purpose of Mirkin, since it would dilute the signal that Mirkin is trying to intensify. Additionally, adding a plurality of Chandler's labels to Mirkin's assay would potentially interfere with the signal emanating from Mirkin's nanoparticles, like the interference observed by Mirkin when a combination of gold and quantum dot label monomers was used in a single assay. Thus, the combination of Mirkin and Chandler would be deemed undesirable by one of ordinary skill in the art.

Accordingly, the combination of Chandler and Mirkin does not suggest the presently claimed invention. There is no suggestion in either reference of the use of single molecules, each containing at least two genedigits, attached to respective anti-genedigits attached to label monomers, to create at least 30 labels with distinguishable signals in a population.

In view of the foregoing, Applicant submits that the rejection under 35 U.S.C. § 103 is in error and should be withdrawn.

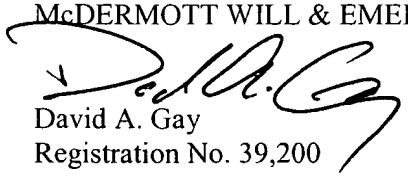
CONCLUSION

Applicant respectfully requests that the Examiner reconsider this application with a view towards allowance. The Examiner is invited to call the undersigned attorney if a telephone call would help resolve any remaining items.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

McDERMOTT WILL & EMERY LLP



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